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## **Diagnosis of MALT lymphoma by conjunctival biopsy: a case report**

Kurz-Levin, Malaika M ; Flury, Renata ; Bernauer, Wolfgang

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Malaika M. Kurz-Levin  
Renata Flury  
Wolfgang Bernauer

## Diagnosis of MALT lymphoma by conjunctival biopsy: a case report

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M.M. Kurz-Levin (✉) · W. Bernauer  
Department of Ophthalmology,  
University Hospital, Frauenklinikstrasse 24,  
CH-8091 Zurich, Switzerland  
Fax +41-1-2554438

R. Flury  
Department of Pathology,  
University Hospital, Zurich, Switzerland

**Abstract** ● **Background:** Most extranodal lymphatic tissue is found in the intestinal mucosa. Together with similarly structured lymphatic tissue at other locations it has been named mucosa-associated lymphatic tissue (MALT). Malignant transformation of such tissue to lymphoma is well known. Although MALT lymphoma has been described in tissue physiologically void of MALT, lymphoma manifestation in the conjunctiva is rare. ● **Methods:** We report a case of a 47-year-old woman who was referred to our clinic for symptomatic treatment and evaluation of severe symptoms of dry eyes. She was thought to suffer from Sjögren's syndrome because of xerophthalmia and xerostomia, as well as massive bilateral swelling of the parotid

gland. Ophthalmological examination revealed marked hyperplasia of the conjunctiva, of which a biopsy was taken. ● **Results:** Histological and immunohistochemical examination of the conjunctival biopsy, together with analysis of gene rearrangement by Southern blot, led to the diagnosis of low-grade B-cell lymphoma of the MALT. ● **Conclusion:** The differential diagnosis of keratoconjunctivitis sicca presenting with conjunctival swelling of unknown origin should include lymphoma, especially since Sjögren's syndrome may be associated with malignant disorders of the lymphatic system. A biopsy of suspicious conjunctival changes can clarify a multisystem disease by providing a tissue diagnosis.

### Introduction

Lymphomas of the parotid gland and the conjunctiva are extranodal lymphomas. These lymphomas arising from tissue other than lymph nodes represent about 40% of non-Hodgkin lymphomas [7]. Most extranodal lymphatic tissue is found in the intestinal mucosa. The structure and function of this tissue resemble those of lymphoid tissue of other mucosae, and it was therefore named mucosa-associated lymphoid tissue (MALT). A lymphoma arising from the MALT in the gastrointestinal tract was first described by Isaacson in 1983 [6]; subsequently lymphomas were observed arising from sites such as the salivary gland, lung and thyroid. It was first suggested in 1989 that some conjunctival lymphomas may belong to the group of MALT lymphomas [10]. Although normal conjunctiva

contains lymphoid tissue consisting of T lymphocytes, B lymphocytes, dendritic cells and, rarely, plasma cells, organized lymphoid tissue in the form of MALT is not regularly found [15].

Low-grade B-cell lymphomas of the MALT tend to remain localized for a long period of time. They usually respond well to the appropriate therapy and hence have a better prognosis than other low-grade lymphomas. If dissemination does occur, it tends to involve other sites with mucosa-associated tissue. Transformation into more aggressive high-grade lymphoma is known to occur [6–9, 13].

Histologically low-grade lymphoma of the MALT simulates the structure of normal MALT. Characteristically, reactive follicles surrounded by a diffuse infiltrate of neoplastic cells are present. These cells resemble centrocytes and have therefore been named centrocyte-like cells (CCL). Aggregates of tumor cells invade the epithe-

lial glandular lining forming the typical lymphoepithelial lesions. Some larger transformed blasts can be found among the CCL. Plasma cell differentiation may be present [6–8, 13].

Differentiation between benign and malignant lymphoid infiltrates in the conjunctiva and the parotid gland, based upon clinical and histological features, can be difficult. The presence of CCL and monoclonality – demonstrated either by detection of immunoglobulin light chain restriction or by showing immunoglobulin gene rearrangement by Southern blot or polymerase chain reaction – has been suggested to be diagnostic for low-grade B-cell lymphoma of MALT [2, 5]. In addition, flow cytometry may be helpful in corroborating the diagnosis of lymphoma and distinguishing the various subtypes. The subclassification may provide information that allows better prediction of the clinical behavior of the disease [12].

We report the case of a patient who presented with swelling of the parotid glands and severe symptoms of dry eyes. The biopsy of conjunctival alterations led to the diagnosis of a lymphoma of the MALT.

## Patient and methods

### Case report

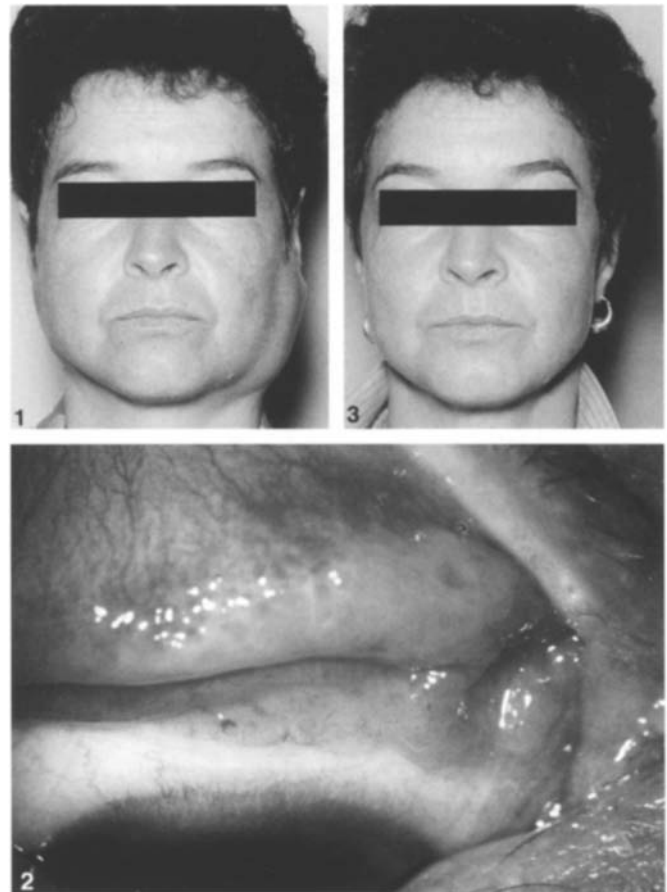
Six months before being referred, a 47-year-old woman noticed an increasing bilateral painless swelling of the parotid gland. She also complained of xerophthalmia with epiphora and xerostomia. Her previous medical history had been unremarkable. A fine needle biopsy of the parotid gland performed by an ENT specialist did not reveal any signs of malignancy. Consequently sialadenitis was suspected to be the cause for the bilateral swelling of the parotid glands, with Sjögren's disease as a possible underlying disorder.

With increasing discomfort due to the xerophthalmia she consulted an ophthalmologist, who found hyperplastic alterations of the conjunctiva. After institution of symptomatic therapy with artificial tears she was referred to our clinic for further evaluation.

On examination she showed bilateral swelling of the parotid glands (left 9×4 cm, right 3×6 cm; Fig. 1). Both eyes had full vision and normal intraocular pressure. The conjunctivae were slightly chemotic, and hyperplastic alterations with some cystic structures were present (Fig. 2). The corneae showed superficial punctate keratopathy and a reduced break-up time in both eyes. The other ophthalmological examinations were normal. We performed a biopsy of the conjunctiva tarsi as well as of the conjunctiva bulbi. Analysis of the tissue revealed a low-grade malignant B-cell lymphoma of the MALT. Further work-up by the oncology service provided the following results: Physical examination revealed no additional pathological findings; laboratory tests were unremarkable except for slight lymphopenia. An X-ray of the chest and a bone marrow examination disclosed no abnormalities. Computed tomography (CT) of the neck, thorax and abdomen showed infiltration of the parotid glands with no further tumor manifestation. Considering the large lymphoma mass, chemotherapy with 25 mg chlorambucil and 100 mg prednisone daily was administered over 5 days. A clinically impressive partial remission was achieved after four cycles of treatment (Fig. 3).

### Histopathology and immunohistochemistry

The unfixed material obtained from the conjunctival biopsy was transported in a humid chamber without delay to minimize tissue artifacts for further work up. Part of the specimen was then snap-fro-



**Fig. 1** Bilateral swelling of the parotid gland at presentation

**Fig. 2** Conjunctiva with hyperplastic alterations, some cystic structures and slight chemosis

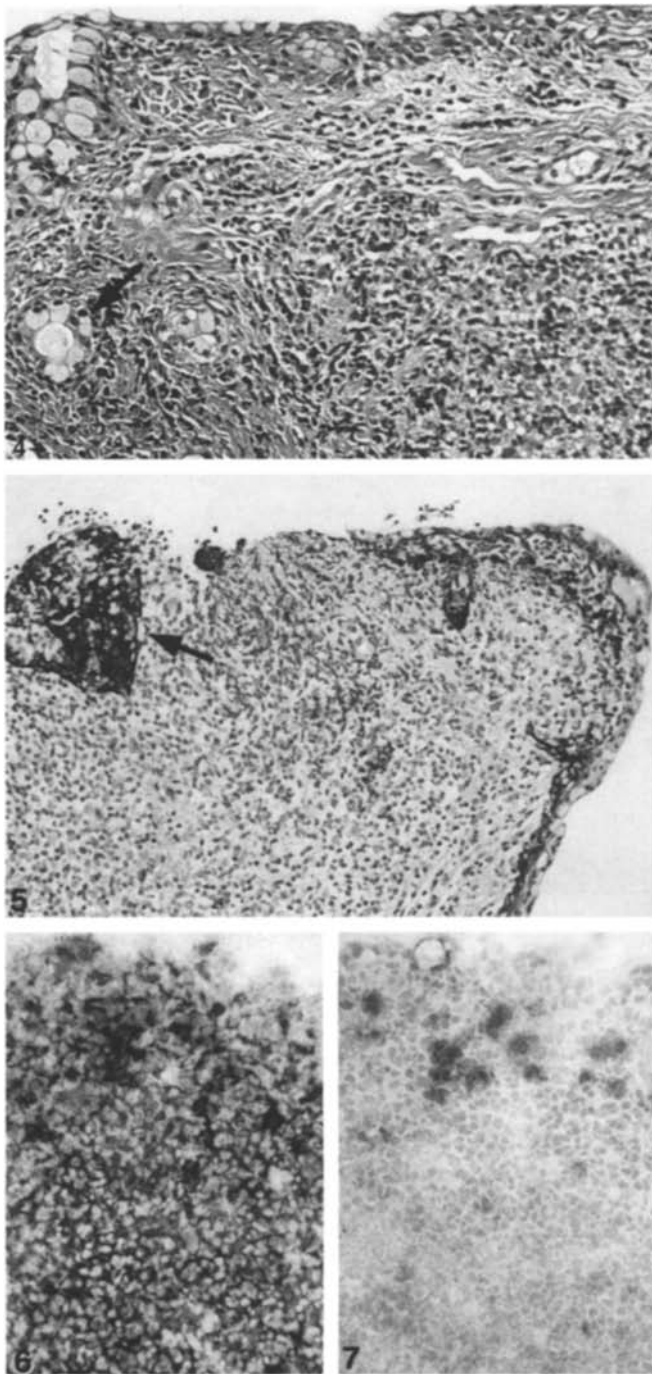
**Fig. 3** Partial remission of parotid gland swelling after four cycles of chemotherapy

zen to  $-70^{\circ}\text{C}$  for subsequent immunohistochemical investigations. The remaining tissue was fixed in formalin and embedded in paraffin wax for conventional histological examination.

For immunohistochemical investigations the diaminobenzidine technique was employed. The following monoclonal mouse antibodies and concentrations were used: CD 45: DAKO M 701, 1:400; CD 20: DAKO M 755, 1:100; CD 3: DAKO M 756, 1:200; CD 5: DAKO M 705, 1:50; kappa: BMA T-1307, 1:50; lambda: BMA T-1304, 1:50.

## Results

The histological examination of the conjunctival biopsy showed a dense monomorphic lymphoid infiltrate, predominantly composed of CCL with scattered larger lymphoid cells (blasts) (Fig. 4). CCL formed typical lymphoepithelial lesions by invasion of the surface epithelium and glandular epithelium (Fig. 5). Immunohistochemical investigations and gene rearrangement were performed on frozen material. The B-cell lineage of the CCL infil-



**Fig. 4** High-power view of the conjunctiva with dense lymphoid infiltrate and penetration of the glandular epithelium (*arrow*) (hematoxylin and eosin,  $\times 200$ )

**Fig. 5** Lymphoepithelial lesion: monomorphic neoplastic centrocyte-like cells infiltrating the surface epithelium of the conjunctiva (*arrows*) (pancytokeratin, Lu 5,  $\times 110$ )

**Figs. 6, 7** Immunohistochemical staining for light-chain immunoglobulins ( $\times 180$ ). **6** Monoclonal expression of lambda in tumor cells. **7** No expression of kappa in tumor cells

trate could be demonstrated immunohistochemically by (CD 45 and) CD 20 positivity, whereas CD 3 and CD 5 were negative. Monoclonality could be demonstrated immunohistochemically by detection of monoclonal cytoplasmic immunoglobulin expression (light-chain lambda restriction) (Figs. 6, 7). Some admixed plasma cells expressed polytypic cytoplasmic immunoglobulin and turned out to be reactive. The resulting immunophenotype therefore supported the morphological diagnosis of low-grade B-cell lymphoma of MALT. In addition, immunoglobulin gene rearrangement was analyzed using Southern blot. Monoallelic clonal rearrangement was demonstrated in the *igH* locus. These results clearly demonstrated the presence of a clonal B-cell population and confirmed the morphological diagnosis of low-grade B-cell lymphoma of the MALT.

### Discussion

The differential diagnosis of conjunctival swelling includes, as well as amyloidosis and granulomatous diseases such as sarcoidosis, disorders of the lymphoid system, particularly lymphoma. Upon conjunctival biopsy our patient was found to have histological and immunohistochemical features consistent with low-grade MALT lymphoma as described in other parts of the body. Tissues well documented to contain lymphomas of the MALT are the gastrointestinal tract, salivary glands, thyroid, lung and thymus. Medeiros and Harris [10] first described a group of orbital and conjunctival lymphomas they suspected of being MALT lymphomas in 1989. In 1990 Bron et al. [1] reported a patient presenting with an indolent tumor of the bulbar conjunctiva and raised the question of a possible MALT origin. Wotherspoon et al. [14] examined biopsies of patients with conjunctival lymphoid infiltrates using histological, immunohistochemical and molecular genetic techniques. They found features of low-grade B-cell lymphoma of the MALT, suggesting that most conjunctival lymphomas are of this type. In the present case we were able to prove the diagnosis of MALT lymphoma of the conjunctiva applying the morphological criteria and immunological methods mentioned above.

The clinical presentation of our case is unusual in that there was bilateral lymphoma of the conjunctivae and the parotid glands. The bilateral parotid gland enlargement was also considered to represent a manifestation of the lymphoma on account of the large mass and the pattern of tissue infiltration as shown on CT. This view is supported by the failure of the laboratory tests to reveal an autoimmune or chronic inflammatory process (see below). An invasive procedure to gain parotid gland tissue was not undertaken. Wotherspoon et al. [14] reported bilateral disease in the absence of dissemination to be common, whereas multifocal MALT lymphoma was rare. It is noteworthy that the hardly invasive conjunctival biopsy clarified the multisystem disorder in this case.

A prominent clinical feature of MALT lymphoma is the tendency to remain localized for a long period of time.

Hoang-Xuan et al. [4] presented a case of scleritis and choroidal infiltrates unresponsive to steroid therapy in which the diagnosis of conjunctival MALT lymphoma was made after some delay. They were not able to differentiate between MALT lymphoma with diffuse scleral infiltration, intraocular low-grade malignant lymphoma with scleroconjunctival involvement, and association of MALT lymphoma with a sclerouveitis of unknown origin.

Before the bilateral hyperplastic alterations of the conjunctivae were discovered, our patient was thought to be suffering from Sjögren's disease with myoepithelial sialadenitis (MESA) causing the swelling of the parotid glands. It is known that in sites usually devoid of MALT, as the conjunctiva is thought to be [15], MALT accumulates in response to autoimmune diseases, such as Sjögren's syndrome in the salivary glands or Hashimoto's thyroiditis. Gastric MALT lymphoma seems to be preceded by infection with *Helicobacter pylori*. In MESA, lymphoid tissue accumulates in the salivary glands in a fashion closely resembling MALT. The association of MESA with Sjögren's syndrome is well known, and it seems to be a common if not even necessary precursor for MALT lymphoma of the salivary gland [2, 5, 11]. In our case, though, we were not able to confirm the presence of Sjögren's syndrome, although multiple laboratory tests were performed (antibodies to double-stranded DNA, to Ro/SSA and to La/SSB were negative).

This case demonstrates the difficulty of distinguishing between benign and malignant disease while relying on the clinical presentation alone. The symmetrical distribution with involvement of both conjunctivae and both parotid glands was suggestive of a benign disorder. Only the biopsy of the conjunctiva revealed the malignant nature of

the disease. This emphasizes the importance of obtaining a tissue sample to confirm a diagnosis. It should be pointed out, however, that routine histology with formalin-fixed tissue allows only suspicion of lymphoma. Unfixed tissue should therefore be available for the pathologist to carry out further diagnostic tests.

In order to confirm a suspected lymphoma, monoclonality in the tissue probe has to be proven. In our case this was performed with immunohistochemical investigations and by analyzing the gene rearrangement with Southern blot. Gene rearrangement of the immunoglobulin occurs when a population of B-cells begins to differentiate. In clonal differentiation, rearrangement of only one allele is present; this is termed allelic exclusion. A monoclonal expansion will therefore have a unique DNA rearrangement pattern which is detected in Southern blot as a distinct band different from the unrearranged form of the gene. For examination of a tissue probe with Southern blot, DNA is extracted from cell suspension and cut with specific restriction enzymes. The digested DNA is size-separated on an agarose gel and transferred to membranes. Hybridization with radiolabeled DNA probes is followed by autoradiography, where in a cell population containing clonal rearrangement a distinct new band is detected [3].

In summary, this case demonstrates: (1) In selected cases of keratoconjunctivitis sicca with conjunctival swelling a conjunctival biopsy should be considered in order to exclude lymphoma. (2) Association of Sjögren's syndrome with a malignant disorder of the lymphatic system is possible. (3) Low-grade B-cell lymphoma of the MALT can arise in the conjunctiva and other sites simultaneously. The diagnosis may be made in the readily accessible conjunctival tissue.

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